REMARKS

Status of the Claims

Claims 1-66 are currently pending in the above-referenced patent application; claims 55, 64, 65, and 66 have been amended. Claim 55 has been amended for clarity to insert "(a)" and "(b)" before each of recited steps. Claim 64, 65, and 66 have been amended to ensue correct antecedent basis. Support for the amendments is found in the specification at page 16, lines 1-2, page 17, lines 4-19, and page 18, lines 22-26.

In the Office Action, the claims are rejected, in various combinations, under 35 U.S.C. § 112, second paragraph, as allegedly indefinite under 35 U.S.C. § 102(b) as allegedly anticipated, and under 35 U.S.C. § 103(a) as allegedly obvious. For the reasons set forth below, each of these rejections is overcome.

The Invention

The present invention is directed to liposome compositions comprising a lipid and a condensing agent-nucleic acid complex encapsulated within the liposome.

Interview Summary

Applicants wish to thank Examiner Kishore for extending the courtesy of the telephonic interviews held on October 13, 2004 and October 14, 2004 with Applicants' representatives Carol Fang and Eugenia Garrett-Wackowski. During this interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. More particularly, the rejection of the claims under 35 U.S.C. § 102(b) as allegedly anticipated in view of WO 95/34647 or WO 98/20857, and under 35 U.S.C. § 103(a) as allegedly obvious in view of WO 95/34647 or WO 98/20857 and Holland *et al.* or Lisziewicz *et al.* was discussed. Applicants explained that the cited references describe nucleic acid-lipid ***complexes*** formed by mixing ***preformed*** liposomes with nucleic acids. Applicants further explained that, in contrast to the cited references, the present claims are directed to liposomal formulations comprising a condensing agent-nucleic acid complex that is ***encapsulated*** in a liposome. The

Examiner agreed that nucleic acid-lipid complexes do not anticipate or render obvious liposomes encapsulating nucleic acid-condensing agent complexes. Applicants thank Examiner Kishore for his time.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim1 11, 41, 58, and 64-66 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection, and address each of the rejections in the order presented by the Examiner

As set forth in MPEP § 2173.02, "[d]efiniteness of claim language, must be analyzed in light of (A) content of the application; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

1. Claims 11, 41, and 58

In making this rejection, the Examiner alleges that it is not clear whether the diameters recited in the claims refer to the complex or the liposomes. A perusal of claims 11, 41, and 58 reveals that each claim expressly recites "wherein said condensing agent lipid complex is about 30 nm to about 60 nm in diameter." Applicants maintain that one of skill in the art would read this recitation as referring to the complex and not to the liposome. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

2. Claim 64

The Examiner has alleged that claim 64 is unclear because the recitation "PEG-ceramide" lacks proper antecedent basis. Claim 64 has been amended to be dependent on claim 60, which recites "PEG-ceramide." Thus, as amended, claim 64 has proper antecedent basis for the recitation "PEG-ceramide." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

3. Claims 65-66

The Examiner has alleged that claims 65-66 are unclear for referring back to step (c) of claim 55. Claim 65 has been amended to delete the recitation to step (c). Claim 66 has been amended to refer to step (b) of claim 55. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-4, 8, 15, 26-27, 32-35, 39, 43, 55, and 57 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 95/34647 and claims 1-8, 12-17, 21-22, 26-39, 42-45, 49, 52-53, 55, 57-58, 62-63, and 65-66 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 98/20857. Applicants respectfully traverse these rejections.

For a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .***There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.***

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

1. Rejection of claims 1-4, 8, 15, 26-27, 32-35, 39, 43, 55, and 57 as allegedly anticipated by WO 95/34647

The Examiner initially alleged that WO 95/34647 anticipates the presently claimed invention because the reference discloses liposomal compositions containing a nucleic acid wherein the nucleic acid is in a complex formed with a histone.

The present invention is directed to liposomal formulations comprising a lipid and a condensing agent-nucleic acid complex encapsulated within the liposome.

As discussed with the Examiner, WO 95/34647 describes a ***complex*** comprising a preformed cationic liposome (*i.e.*, Lipofectin) and nucleic acid bound to a targeting peptide (*e.g.*, a histone protein). In contrast to the presently claimed liposomal formulations, the nucleic acid portion of the complex described in WO 95/34647 is not encapsulated in the liposome. As explicitly set forth in WO 95/34647, ***preformed*** cationic liposomes are mixed with a peptide-plasmid DNA complex to form a liposome-nucleic aid ***complex*** (*see*, *e.g.*, page 17, line15 to page 20, line 19). There is no hint or suggestion in WO 95/34647 that the nucleic acid-peptide ***complex*** is ***encapsulated*** within the liposome. In contrast, the presently claimed liposomal formulations comprise condensing agent complexes ***encapsulated*** in liposomes (*see*, *e.g.*, page 13, lines 31 to page 14, line 3 and page 23, lines 17-33). As disclosed in the instant specification, the claimed invention is directed toward lipid encapsulation of a condensing agent-nucleic acid complex (*see*, *e.g.*, page 8, lines 15-18 and page 13, lines 32-33). The encapsulated nucleic acids have several superior properties including, *inter alia*, greater resistance to enzymatic degradation (*see*, page 8, line 16). Since WO 95/34647 does not disclose or suggest encapsulation of nucleic acids in a liposome, at least one element of the claimed invention is absent from the cited reference. Thus, WO 95/34647 does not anticipate the present invention. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

2. Rejection of claims 1-8, 12-17, 21-22, 26-39, 42-45, 49, 52-53, 55, 57-58, 62-63, and 65-66 as allegedly anticipated by WO 98/20857

The Examiner also initially alleged that WO 98/20857 anticipates the presently claimed invention because the reference discloses liposomal formulations containing nucleic acid complexes, wherein the nucleic acid is reacted with an organic polycation to produce a condensed nucleic acid.

As discussed with the Examiner, WO 98/20857 describes methods for the preparation of liposome-nucleic acids ***complexes***. According to the methods of WO 98/20857, nucleic acids are added to a mixture of ***preformed*** liposomes (*See, e.g.*, page 4, lines 5-14 and page 34, lines 10-20 and page 35, lines 1-18). More particularly, as explicitly set forth in WO 98/20857, the liposomes are preformed prior to contacting them with a nucleic acid (*see, e.g.*, page 34, lines 10-21 and page 35, lines 1-21). In some cases, the nucleic acid is condensed with a condensing agent prior to contact with the preformed liposomes to form a nucleic acid-liposome ***complex*** (*see, e.g.*, page 35, lines 16-18). During the interview, the Examiner initially expressed concern that a condensing agent would neutralize the anionic charge on the nucleic acid, thus preventing formation of a further complex between the condensing agent-nucleic acid complex and the preformed cationic liposome. However, as discussed with the Examiner, a perusal of WO 98/20857 reveals that the ratio of condensing agent:nucleic acid used (*i.e.*, 7.25 ng-725 ng condensing agent to 1 μg DNA) is not sufficient to completely neutralize the anionic charge on the nucleic acid (*see, e.g.*, page 35,line 17). During the interview, the Examiner agreed that the condensing agent-nucleic acid complex described in WO 98/20857 will form a complex with the preformed liposome whereby the nucleic acid portion of the complex is not encapsulated in the liposome portion of the complex. Thus, compositions prepared as described in WO 98/20857 would not comprise nucleic acids ***encapsulated*** in liposomes and at least one element of the presently claimed invention is absent from the cited reference. Therefore, WO 98/20857 does not anticipate the presently liposomal formulations.

Accordingly, Applicants urge the Examiner to withdraw the rejections under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103(a)

The claims have been rejected, in various combinations, under 35 U.S.C. § 103(a) over a number of different references. In response, Applicants respectfully traverse each of the §103 obviousness rejections.

> As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must

> be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. As explained herein below in connection with each of the § 103(a) obviousness rejections, Applicants assert that a *prima facie* case of obviousness has not been established for at least the following reason: the cited art references do not teach or suggest all the claim limitations.

1. Rejection of claims 11-14, 23-31, 31-42, 49-53, 56, 58, 62-63, and 65-66 as allegedly obvious over WO 98/20857

The Examiner initially alleged that the presently claimed invention is obvious in view of WO 98/20857. In particular, the Examiner alleged that WO 98/20857 teaches sizes of liposomes encompassed by the presently pending claims, varying the nucleic acid:cationic lipid ratio, and the use of PEG as a bilayer stabilizing compound and concluded that the presently claimed compositions and methods are obvious in view of these disclosures. As discussed in detail above, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex ***encapsulated*** in a liposome. In contrast, the disclosure of WO 98/20857 discloses nucleic-acid lipid complexes. The nucleic acid portion of the complexes described in WO 98/20857 is not encapsulated in the lipid portion. Thus, WO 98/20857 does not teach or suggest condensing agent-nucleic acid complex ***encapsulated*** in a liposome. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over WO 98/20857. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

2. Rejection of claims 17-20, 28-29, 45-48, 53-54, 60, and 63-64 as allegedly obvious over WO 95/34647 or WO 98/20857 further in view of Holland *et al.* (U.S. Patent No. 5,885,613)

In making this rejection, the Examiner acknowledges that neither WO 95/34647 nor WO 98/20857 disclose PEG-ceramide and cites Holland as disclosing liposomal formulations comprising PEG-ceramide. The Examiner concludes that the presently claimed liposomal compositions would have been obvious over WO 95/34647 or WO 98/20857 further in view of Holland *et al.*

As discussed in detail above, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex ***encapsulated*** in a liposome. In contrast, the disclosures of WO 95/34647 and WO 98/20857 each disclose nucleic-acid lipid complexes. The nucleic acid portion of the complexes described in WO 95/34647 and WO 98/20857 is not encapsulated in the lipid portion. Thus, the cited references alone, or in combination, do not teach or suggest the presently claimed liposomal condensing agent-nucleic acid complex ***encapsulated*** in a liposome. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over WO 95/34647 and WO 98/20857. Moreover, as discussed with the Examiner during the interview, Holland *et al.*'s disclosure of PEG-ceramide does not remedy the defect in either of the cited references. Thus, the presently claimed invention is nonobvious and patentable over the combination of WO 95/34647 or WO 98/20857 further in view of Holland *et al.*

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

3. Rejection of claims 8-10, 23-25, 39-40, 50-51 and 61 as allegedly obvious over WO 95/34647or WO 98/20857, further in view of Lisziewicz *et al.* (U.S. Patent No. 6,420,176)

In making this rejection, the Examiner acknowledges that neither WO 95/34647 nor WO 98/20857 disclose the use of polythethylenimine and cites Lisziewicz *et al.* as disclosing

polyethylenimine as a nucleic acid condensing agent. The Examiner concludes that the presently claimed liposomal compositions would have been obvious over WO 95/34647 or WO 98/20857 further in view of Lisziewicz *et al.*

As discussed in detail above, the presently claimed invention is directed to compositions comprising a nucleic-acid-condensing agent complex ***encapsulated*** in a liposome. The disclosures of WO 95/34647 and WO 98/20857 each disclose nucleic-acid lipid ***complexes***. In contrast to the presently claimed invention, the nucleic acid portion of the complexes described in WO 95/34647 and WO 98/20857 is not encapsulated in the lipid portion. Thus, the cited references alone, or in combination, do not teach or suggest condensing agent-nucleic acid complex ***encapsulated*** in a liposome. Absent such a teaching or suggestion, the compositions and methods of the presently claimed invention are nonobvious, and thus patentable over WO 95/34647 and WO 98/20857. Moreover, as discussed with the Examiner during the interview, Lisziewicz *et al.*'s disclosure of polyethylenimine does not remedy the defect in either of the cited references. Thus, the presently claimed invention is nonobvious and patentable over the combination of WO 95/34647 or WO 98/20857 further in view of Lisziewicz *et al.*

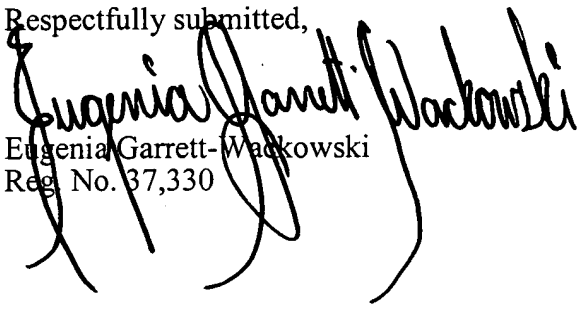
Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



Eugenia Garrett-Wadkowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CAF:caf

60385676 v1